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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/881,721	06/18/2001	Yair Reisner	01/21720	7956

7590 01/12/2005

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EXAMINER	
BELYAVSKYI, MICHAIL A	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 01/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/881,721	REISNER, YAIR	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

-- The MAILING DATE f this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 2, 5, 7, 9- 14, 16-17 , 19- 55, 59-66 and 70-80* is/are pending in the application.

4a) Of the above claim(s) *22-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 5, 7, 9- 14, 16-17, 19-21, 46-55, 59-66 and 70-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/29/04 has been entered.

Claims 1, 2, 5, 7, 9- 14, 16-17 , 19- 55, 59-66 and 70-80 are pending.

Claims 22-45 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

Claims 1, 2, 5, 7, 9- 14, 16-17, 19-21, 46-55, 59-66 and 70-80 drawn to a method of inducing tolerance to transplant and method of transplanting a transplant, comprising a step of administering to the recipient a dose of tolerance-inducing cells are under consideration in the instant application.

In view of the amendment, filed 10/29/04 the following rejection remains:

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1, 2, 5, 7, 9- 14, 16-17, 19-21, 46-55, 59-66 and 70-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 5,806,529 in view of Bachar-Lustig E et al. (Blood, 1999, v 94, pp 3212-3221) , or Mobest D et al. (Biotechnology and Bioengineering, 1998, v. 60 pp. 341-347), or Vavrova et al. (Hematol.Cell Ther. 1999, v.41 pp105-112) for the same reasons set forth in the previous Office Action, mailed 05/03/04.

Applicant's arguments, filed 10/29/04 have been fully considered, but have not been found convincing.

Applicant asserts that: (i) amended independent claims 1 and 12 now recites a method of inducing tolerance in a recipient comprising administration to the recipient of a donor-derived cultured HPC population which is composed of at least 83.5 % cells displaying a characteristic associated with a myeloid phenotype that are clearly not rendered obvious by any of the cited combination of the primary and secondary references; (ii) very unexpectedly cultured HPC composed of at least 832.5 % myeloid cells have the ability not only to retains any significant capacity to induced donor-specific tolerance relative to non-cultured HPC, but further that such capacity optimally enhanced per cell relative to non-cultured HPC; (iii) Declaration by Dr. Reisner under 37 CFR 1.132 clearly stating that " it had never been documented that a human donor-derived cultured CD34+ cell population composed of at least 83.5 % myeloid cells could possess enhanced veto activity per cell relative to a non-cultured human donor derived CD34+ cell population.

It appears that Applicant and the Examiner differ on the interpretation of the prior art. It is the Examiner position that combination of primary and secondary references rendered obvious of the claimed invention.

US Patent '529 teaches a method of inducing tolerance to a transplant during bone marrow transplantation comprising administering HPC cells derived from allogenic donor (see entire document, Abstract in particular) . The '529 Patent also teaches that host patient is conditioned prior to the transplantation of hematopoietic stem cells (HPC) . Conditioning may be carried out under sublethal, lethal or supralethal conditions (see column 3, lines 51-60 in particular). The '529 Patent also teaches that donor and recipient are both humans (see Example 1 in particular). The '529 Patent also teaches that said method enable engraftment of MHC-mismatched transplants (see column 2, lines 36-42 in particular).

The '529 Patent does not teaches that said HPC cells, derived from the donor are *ex vivo* culturing under growth conditions suitable for generating a cultured HPC population having a enhancing veto activity wherein cell displaying a characteristic associated with a myeloid phenotype make up to at least 83.5 % prior to transplantation of the transplant.

Bachar-Lustig E. et al., teach that it is possible to culture HPC cells under growth conditions, suitable for inducing or enhancing tolerance-inducing activity of CD34+ cells by expanding *in vitro* the CD34+ cells and use them for transplantation (see entire document, abstract and page 3220 in particular). Applicant's attention is drawn to left column on page 3220, wherein Bachar-Lustig et al., explicitly teaches that " it may be possible to expand in vitro the CD34+ cells possessing veto activity and use them together with a small number of pluripotential cells for transplantation."

It is also noted that the statement in Declaration under 37 CFR 1.132 by co-inventor of the instant application Dr. Reisner : " it had never been documented that a human donor-derived cultured CD34+ cell population composed of at least 83.5 % myeloid cells could possess enhanced veto activity per cell relative to a non-cultured human donor derived CD34+ cell population" is not in consistency with the statement of the prior art reference of Bachar-Lustig E. et al, wherein Dr. Reisner is co-author. As has been discussed, supra said reference clearly stated that " it may be possible to expand in vitro the CD34+ cells possessing veto activity and use them together with a small number of pluripotential cells for transplantation." (see page 3220 left column in particular). Clearly one of ordinary skill in the art at the time the invention was made would be able to understand that expanding human CD34+ cells *ex-vivo* under condition that generate veto activity will result in a cultured HPC population possessing enhanced veto activity per cells relative to a non-cultured cell population as a result of expansion in cell numbers and differentiation of cells into CD33+ myeloid phenotype cells . It would be immediately obvious to one of ordinary skill in the art at the time the invention was made that purified population of said expanded cells possessing veto activity will result in a cell population composed of at least 83,5 percent myeloid cells. Moreover, Applicant acknowledge that the prior art method of expansion of HPC cells will result in generation of Cd33+Cd34+ cells i.e the cells displaying a characteristics associated with a myeloid phenotype (see Applicant's response filed on 03/22/04).

Mobest et al., teach *ex vivo* expansion of human CD34+ hematopoietic progenitor cells under condition suitable for inducing differentiation of said cells into $CD33^+$ myeloid phenotype cells (see entire document, Abstract in particular). Mobest et al., also teach that successful ex vivo culture and amplification of human CD34+ hematopoietic progenitor cells that would differntiate into $CD33^+$ myeloid phenotype cells offers the possibility of additional graft manipulation steps, e.g. depletion or elimination of contaminating tumor cells in Autologous grafts, amplification of bone marrow-repopulating hematopoietic cells, generation of immune effector cells, or genetic manipulation of stem cells (see page 341 in particular). The growth condition taught by Mobest et al. are the same as to growth conditions disclosed in the instant specification (see Materials and Method in particular). It would be obvious to a person of ordinary skill in the art at the time the invention was made that the CD34+ HPC obtained and grown under the same conditions as disclosed in the instant specification would also be induced to differentiate into myeloid CD33+ cells with the same functional property as HPC recited in the instant claims absent a showing of unobvious property. In addition, Mobest et al. teach the methodology of analyzing the role of individual components of culturing medium for inducing myeloid differentiation of cultured HPSc (see page 344 in particular). Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

Vavrova et al. teach a method of *ex vivo* expansion and differentiation of human HPC cells under growth conditions suitable for inducing or enhancing veto activity in at least a portion of said HPC cells and inducing differentiation of said HPC cells into $CD33^+$ myeloid phenotype cells (see entire document, Abstract and page 106 in particular). Vavrova et al., teach that *ex vivo* expansion of HPC would benefit studies including accelerated engraftment, reduced risk of infection, smaller stem cell harvest and improved effectiveness of genetically modified stem cells. The growth condition taught by Vavrova et al. are the same as to growth conditions disclosed in the instant specification (see Materials and Method and Table 3 in particular). It would be obvious to a person of ordinary skill in the art at the time the invention was made that the CD34+ HPC obtained and grown under the same conditions as disclosed in the instant specification would also be induced to differentiate into myeloid CD33+ cells with the same functional property as HPC recited in the instant claims absent a showing of unobvious property.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of Bachar-Lustig E et al., or Mobest D et al., or Vavrova et al., to those of The '529 Patent, to obtain a claimed method of inducing tolerance to a transplant or a method of transplanting a transplant from a donor to a recipiet comprising a step of *ex vivo* culturing HPC, derived from the donor under growth conditions suitable for inducing or enhancing veto activity in at least a portion of said HPC cells and inducing differentiation of said HPC cells into $CD33^+$ myeloid phenotype cells prior to transplantation of the transplant.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because successful *ex vivo* culture and amplification of human CD34+ hematopoietic progenitor cells under growth conditions that would stimulated to differentiation of the said cells into $CD33^+$ myeloid phenotype cells prior to transplantation of the transplant offers additional possibility and would be beneficial in accelerated engraftment, reduced risk of infection, additional graft manipulation steps, e.g. depletion or elimination of contaminating tumor cells in autologous grafts, amplification of bone marrow-repopulating hematopoietic cells, generation of immune effector cells, or genetic manipulation of stem cells as taught by Bachar-Lustig E et al., or Mobest D et al., or Vavrova et al. These *ex vivo* cultured , amplified and differentiated CD34+ hematopoietic progenitor cells can be further used in a method of inducing tolerance to a transplant during bone marrow transplantation taught by the '529 Patent. Since the growth condition taught by Bachar-Lustig E et al., or Mobest D et al., or Vavrova et al., are the same as to growth conditions disclosed in the instant specification it would be obvious to a person of ordinary skill in the art at the time the invention was made that the CD34+ HPC obtained and grown under the same conditions as disclosed

in the instant specification would also be induced to differentiate into myeloid CD33+ cells with the same functional property as HPC recited in the instant claims absent a showing of unobvious property.

Claims 46 and 47 are included because it would be conventional and within the skill of the art to identify the optimum culturing conditions suitable for inducing myeloid differentiation of cultured HPSc. In addition, Mobest et al. teach the methodology of analyzing the role of individual components of culturing medium for inducing myeloid differentiation of cultured HPSc (see page 344 in particular). Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

Claims 50-55 and 61-66 are included because the claimed functional limitation would be an obvious properties of the known and referenced method of *ex-vitro* culturing of HPS. because that both the prior art and applicant administer the same method of *ex-vitro* culturing of HPS. When the prior art method is the same as a method described in the specification, it can be assumed the method will obviously perform the claimed process absent a showing of unobvious property.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

4. No claim is allowed.

5. It is noted that the Specification at page 48 disclosed a Table 1 comprising text in foreign language that is not appropriate for applications filed in US.

6. This is a RCE of applicant's earlier Application No. 09/881721 . All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/ 272-0840 The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/ 272-0841 .

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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